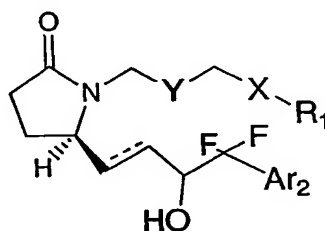


WHAT IS CLAIMED IS:

1. A method for treating ocular hypertension or glaucoma comprising administration to a patient in need of such treatment a therapeutically effective amount of a compound of formula I:



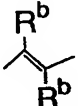
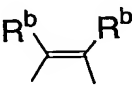
FORMULA I

10

or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug or mixture thereof, wherein,

X is $(CH_2)_n$, O or S;

15

Y represents $(C(R^b)_2)_n$, triple bond,  or  ;

20

R_1 represents hydroxy, CN, CHO, $NHSO_2R_6$, $CONHSO_2R_6$, $CON(R_6)_2$ hydroxymethylketone, $(CH_2)_pCO_2R_6$, $(CH_2)_nSO_3R_6$, C1-4 alkoxy, or $(CH_2)_nC_5$ -10heterocyclyl, said heterocyclyl unsubstituted or substituted with 1 to 3 groups of R_a and optionally containing an acidic hydroxyl group, with the proviso that when X is a bond R_1 is not $(CH_2)_pCO_2R_6$, C1-4 alkoxy, $-(CH_2)_nNR_6R_7$, CHO, $NHSO_2R_6$, $CONHSO_2R_6$, $CON(R_6)_2$, or hydroxymethylketone;

25 R_2 and R_3 independently represents hydrogen, or C1-4 alkyl;

R₆ and R₇ independently represents hydrogen, or C₁₋₆ alkyl, C₃₋₁₀ cycloalkyl, (CH₂)_pC₆₋₁₀aryl, (CH₂)_pC₅₋₁₀heterocyclyl, CR²R³OC(O)OC₃₋₁₀cycloalkyl or CR²R³OC(O)O C₁₋₁₀alkyl;

- 5 Ar₂ independently represent (CH₂)_mC₆₋₁₀aryl, (CH₂)_mC₅₋₁₀heteroaryl, (CH₂)_mC₃₋₁₀ heterocycloalkyl, (CH₂)_mC₃₋₈ cycloalkyl said cycloalkyl, heterocycloalkyl, aryl or heteroaryl unsubstituted or substituted with 1-3 groups of R_a;

10 R_a represents C₁₋₆ alkoxy, C₁₋₆ alkyl, CF₃, nitro, amino, cyano, C₁₋₆ alkylamino, or halogen;

R^b independently represents H, halogen, C₁₋₆ alkyl, C₃₋₆ cylcoalkyl or

15 \equiv represents a double or single bond;

p represents 1-3;

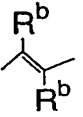
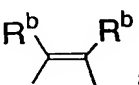
n represents 0-4; and

20 m represents 0-8.

2. The method according to claim 1 wherein R₁ is CN, (CH₂)_nC₅₋₁₀heterocyclyl, (CH₂)_pCO₂R₆ or (CH₂)_nSO₃R₆, said heterocyclyl
25 unsubstituted or substituted with 1 to 3 groups of R_a and all other variables are as originally described.

3. The method according to claim 2 wherein X and Y are (CH₂)_n.

- 30 4. The method according to claim 1 wherein Y is a double bond as

described by  or  and all other variables are as originally described.

5. The method according to claim 1 wherein R_1 is $(CH_2)_n C_5-10$ heterocyclyl, said heterocyclyl unsubstituted or substituted with 1 to 3 groups of R_a , X is $(CH_2)_n$, and Y is $(CH_2)_n$ or $C(halo)_2$.

6. The method according to claim 1 wherein R_1 is
 5 $(CH_2)_p CO_2 R_6$, X is $(CH_2)_n$, and Y is $(CH_2)_n$.

7. The method according to claim 1 wherein Ar_2 is $(CH_2)_m C_6-10$ aryl, said aryl unsubstituted or substituted with 1 to 3 groups of R_a and all other variables are as originally described.

8. The method according to claim 1 wherein R_1 is a tetrazole
 10 unsubstituted or substituted with an R_a group X is $(CH_2)_n$, and Y is $(CH_2)_n$, $C(halo)_2$

or a double bond as described by  or .

9. The method according to claim 1 wherein Ar_2 is a phenyl
 unsubstituted or substituted with 1 to 3 groups of R_a , R_1 is tetrazolyl, said tetrazolyl
 unsubstituted or substituted with a R_a group and phenyl is unsubstituted or substituted
 15 with 1-3 groups of R_a , and all other variables are as originally described.

10. The method according to claim wherein the compound is:
 (5*R*)-5-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-{4-[(1-methyl-1*H*-
 tetrazol-5-yl)]butyl}pyrrolidin-2-one,
 4-[(2*R*)-2-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-
 20 yl]butyl cyanate,
 3-[(2*R*)-2-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-
 yl]butyl]propanoic acid,
 [4-[(2*R*)-2-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-
 yl]butyl]methanesulfonic acid,
 25 (5*R*)-5-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-{4-[1*H*-tetrazol-5-
 ylmethyl]butyl}pyrrolidin-2-one,
 [4-[(2*R*)-2-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-
 yl]butyl]acetic acid,
 (5*R*)-5-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-{4-[(1-methyl-1*H*-
 30 tetrazol-5-yl)thio]butyl}pyrrolidin-2-one,
 (5*R*)-5-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-[4-(1*H*-tetrazol-5-
 ylthio)butyl]pyrrolidin-2-one,

- 3-[4-{(2*R*)-2-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}butyl)thio]propanoic acid,
 [4-{(2*R*)-2-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}butyl)thio]methanesulfonic acid,
- 5 (5*R*)-5-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-[4-(methylsulfonyl)butyl]-pyrrolidin-2-one,
 [4-{(2*R*)-2-[(1*E*)-3-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}butyl)thio]acetic acid,
 (5*R*)-5[(1*E*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-1-[6-(1*H*-tetrazol-5-yl)hexyl]pyrrolidin-2-one ,
- 10 7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}heptanoic acid,
 isopropyl 7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}heptanoate,
- 15 7-{(2*S*)-2-[(3*R*)-4,4-difluoro-3-hydroxy-4-phenylbutyl]-5-oxopyrrolidin-1-yl}heptanoic acid,
 (5*Z*)-7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}hept-5-enoic acid,
 isopropyl (5*Z*)-7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}hept-5-enoate,
- 20 7-{(2*R*)-2-[(1*E*,3*R*)-4-(3-chlorophenyl)-4,4-difluoro-3-hydroxybut-1-enyl]-5-oxopyrrolidin-1-yl}heptanoic acid,
 isopropyl 7-{(2*R*)-2-[(1*E*,3*R*)-4-(3-chlorophenyl)-4,4-difluoro-3-hydroxybut-1-enyl]-5-oxopyrrolidin-1-yl}heptanoate,
- 25 7-((2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-[3-(trifluoromethyl)phenyl]but-1-enyl]-5-oxopyrrolidin-1-yl)heptanoic acid,
 isopropyl 7-((2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-[3-(trifluoromethyl)phenyl]but-1-enyl]-5-oxopyrrolidin-1-yl)heptanoate,
 cyclopentyl 7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}heptanoate,
- 30 7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-3-methyl-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}heptanoic acid,
 isopropyl 7-{(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-3-methyl-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}heptanoate,

- isobutyl 7-[(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl]heptanoate,
cyclohexyl 7-[(2*R*)-2-[(1*E*,3*R*)-4,4-difluoro-3-hydroxy-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl]heptanoate,
- 5 (5*R*)-5-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-{4-[(1-methyl-1*H* – tetrazol-5-yl)]butyl}pyrrolidin-2-one,
4-{(2*R*)-2-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}butyl cyanate,
3-[4-{(2*R*)-2-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-
- 10 1-yl}butyl]propanoic acid,
[4-{(2*R*)-2-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}butyl]methanesulfonic acid,
(5*R*)-5-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-{4-[1*H*-tetrazol-5-ylmethyl]butyl}pyrrolidin-2-one,
- 15 [4-{(2*R*)-2-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}butyl]acetic acid,
(5*R*)-5-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-{4-[(1-methyl-1*H* – tetrazol-5-yl)thio]butyl}pyrrolidin-2-one,
(5*R*)-5-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-[4-(1*H* – tetrazol-5-
- 20 ylthio)butyl]pyrrolidin-2-one,
3-[4-{(2*R*)-2-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}butyl]thio]propanoic acid,
[4-{(2*R*)-2-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}butyl]thio]methanesulfonic acid,
- 25 (5*R*)-5-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-1-[4-(methylsulfonyl)butyl]-pyrrolidin-2-one,
[4-{(2*R*)-2-[(1*E*)-(3*R*)-hydroxy-4,4-difluoro-4-phenylbut-1-enyl]-5-oxopyrrolidin-1-yl}butyl]thio]acetic acid, or
(5*R*)-5-[(1*E*)-4,4-difluoro-(3*R*)-hydroxy-4-phenylbut-1-enyl]-1-[6-(1*H*-tetrazol-5-
- 30 yl)hexyl]pyrrolidin-2-one, a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug, or mixture thereof.

11. A method according to claim 1, which is administered in a topical formulation as a solution or suspension.

12. A method according to claim 1 wherein a second active ingredient belonging to the group consisting of: β -adrenergic blocking agent, parasympatho-mimetic agent, sympathomimetic agent, carbonic anhydrase inhibitor, Maxi-K channel blocker, and a prostaglandin, hypotensive lipid, neuroprotectant, and 5-HT₂ receptor agonist is added to the topical formulation.

13. A method according to claim 12 wherein the β -adrenergic blocking agent is timolol, betaxolol, levobetaxolol, carteolol, or levobunolol; the parasympathomimetic agent is pilocarpine; the sympathomimetic agent is epinephrine, brimonidine, iopidine, clonidine, or para-aminoclonidine, the carbonic anhydrase inhibitor is dorzolamide, acetazolamide, metazolamide or brinzolamide; the prostaglandin is latanoprost, travaprost, unoprostone, rescula, or S1033, the hypotensive lipid is lumigan, the neuroprotectant is eliprodil, R-eliprodil or memantine; and the 5-HT₂ receptor agonist is 1-(2-aminopropyl)-3-methyl-1H-imidazol-6-ol fumarate or 2-(3-chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine.

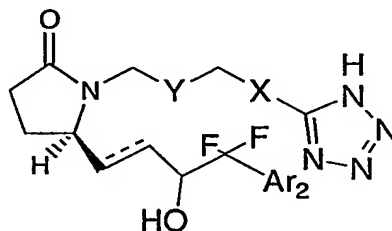
14. A method for treating macular edema, macular degeneration, treating dry eye, increasing retinal and optic nerve head blood velocity, increasing retinal and optic nerve oxygen tension or providing a neuroprotection comprising administration to a patient in need of such treatment a pharmaceutically effective amount of a compound of formula I as recited in claim 1

15. The method according to Claim 14 wherein the compound of formula I is applied as a topical formulation and an active ingredient belonging to the group consisting of β -adrenergic blocking agent, parasympatho-mimetic agent, sympathomimetic agent, carbonic anhydrase inhibitor, Maxi-K channel blocker and a prostaglandin, hypotensive lipid, neuroprotectant, and 5-HT₂ receptor agonist is added to the formulation.

16. A method according to claim 15 wherein the the β -adrenergic blocking agent is timolol, betaxolol, levobetaxolol, carteolol, or levobunolol; the parasympathomimetic agent is pilocarpine; the sympathomimetic agent is epinephrine brimonidine, iopidine, clonidine, or para-aminoclonidine, the carbonic anhydrase inhibitor is dorzolamide, acetazolamide, metazolamide or brinzolamide; the prostaglandin is latanoprost, travaprost, unoprostone, rescula, or S1033, the

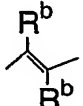
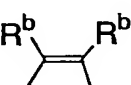
hypotensive lipid is lumigan, the neuroprotectant is eliprodil, R-eliprodil or memantine; and the 5-HT₂ receptor agonist is 1-(2-aminopropyl)-3-methyl-1H-indazol-6-ol fumarate or 2-(3-chloro-6-methoxy-indazol-1-yl)-1-methyl-ethylamine.

- 5 17. A compound of structural formula I:



I

- 10 or a pharmaceutically acceptable salt, enantiomer, diastereomer, pro drug or mixture thereof, wherein
X is (CH₂)_n, O or S;

Y represents (C(R^b)₂)_n, triple bond,  or  ;

- 15 Ar₂ independently represent (CH₂)_mC₆₋₁₀aryl, (CH₂)_mC₅₋₁₀heteroaryl, (CH₂)_mC₃₋₁₀ heterocycloalkyl, (CH₂)_mC₃₋₈ cycloalkyl said cycloalkyl, heterocycloalkyl, aryl or heteroaryl unsubstituted or substituted with 1-3 groups of R_a;

- 20 R_a represents C₁₋₆ alkoxy, C₁₋₆ alkyl, CF₃, nitro, amino, cyano, C₁₋₆ alkylamino, or halogen;

R^b independently represents H, halogen, C₁₋₆ alkyl, C₃₋₆ cycloalkyl or

- 25 --- represents a double or single bond;

n represents 0-4; and

m represents 0-8.

18. The compound according to claim 17 wherein X and Y are $(CH_2)_n$, \equiv represents a double bond; and AR_2 is phenyl.

19. The compound according to claim 18 wherein X is $(CH_2)_n$ and n is 1 and Y is $(CH_2)_n$ and n is 3.

20. Use of a compound of formula I, as defined in any one of claims 1 to 10, or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug, or mixture thereof, in the manufacture of a medicament for treating hypertension or glaucoma.

21. A pharmaceutical composition for treating hypertension or glaucoma comprising a therapeutically effective amount of a compound of formula I, as defined in any one of claims 1 to 10, or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug, or mixture thereof, in association with a pharmaceutically acceptable carrier.

22. A composition according to claim 21 in a form for topical administration as a solution or suspension and further comprising a second active ingredient as defined in claim 12 or 13.

23. Use of a compound of formula I, as defined in any one of claims 1 to 10, or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug, or mixture thereof, in the manufacture of a medicament for treating macular edema, macular degeneration, dry eye, increasing retinal and optic nerve velocity, increasing retinal and optic nerve oxygen tension or providing a neuroprotection.

24. A pharmaceutical composition for treating macular edema, macular degeneration, dry eye, increasing retinal and optic nerve velocity, increasing retinal and optic nerve oxygen tension or providing a neuroprotection comprising a therapeutically effective amount of a compound of formula I, as defined in any one of claims 1 to 10, or a pharmaceutically acceptable salt, enantiomer, diastereomer, prodrug, or mixture thereof, in association with a pharmaceutically acceptable carrier.

25. A composition according to claim 24 in a form for topical administration and further comprising an active ingredient as defined in claim 15 or 16.

26. A compound of claim 17, 18 or 19 for use in medicinal therapy.